

999,394



# PATENT SPECIFICATION

NO DRAWINGS

999,394

Date of Application and filing Complete Specification: Aug. 2, 1961.

No. 28120/61.

Application made in United States of America (No. 46911) on Aug. 2, 1960.

Application made in United States of America (No. 73490) on Dec. 5, 1960.

Application made in United States of America (No. 80007) on Jan. 3, 1961.

Application made in United States of America (No. 110,320) on May 16, 1961.

Application made in United States of America (No. 112,751) on May 26, 1961.

Complete Specification Published: July 28, 1965.

© Crown Copyright 1965.

Index at acceptance:—A2 B(J2, J3F2); A5 B2R1

Int. Cl.:—A 23 k 1/16 // A 61 k

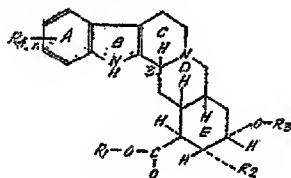
## COMPLETE SPECIFICATION

### New Animal Feed and Drink Preparations

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

5. The present invention is concerned with new animal feed and drink preparations, which have a quieting effect and bring about a better food conversion.

The present invention provides an animal feed or drink preparation which comprises a compound of the general formula I



I

10 or an N - oxide thereof or a physiologically tolerable salt of either of these compounds, in which formula R<sub>1</sub> represents an alkyl group or an alkoxy - alkyl group, R<sub>2</sub> represents a methoxy group, R<sub>3</sub> represents an alkyl group or a hydroxy - alkyl group, and R<sub>4</sub> represents a hydrogen atom or an alkoxy group, in admixture or conjunction with a solid feedstuff or water.

15 The alkyl group represented by the symbol R<sub>1</sub> in formula I advantageously contains 1 to 10 carbon atoms, preferably 1 to 4 carbon atoms, such as methyl, ethyl, n - propyl, isopropyl, n - butyl, iso - butyl or secondary butyl, as well as n - pentyl, iso - pentyl, n - hexyl or n - heptyl. In an alkoxy - alkyl radical, the alkoxy portion advantageously contains 1 to 4 carbon atoms, and represents, for example, methoxy, ethoxy, n - propoxy, iso - propoxy or n - butoxy. The alkyl portion bearing the afore-  
20 said alkoxy group contains at least 2, but preferably 2 or 3, carbon atoms, and separates this group from the ester oxygen atom by at least 2 carbon atoms; it therefore, represents, for example, 1:2 - ethylene, 1:2-, 2:3- or 1:3 - propylene or 1:4- butylene.

25 In the group represented by R<sub>2</sub> bound to the oxygen atom in the 18-position the alkyl group advantageously contains 1 to 10, but preferably 1 to 7, carbon atoms, for example those mentioned above. In a hydroxy - alkyl group the hydroxyl group is separated from the 18—O - atom by at least 2 carbon atoms; it is particularly 2-hydroxy - ethyl, 2- or 3 - hydroxy - propyl, 4 - hydroxy - butyl or 5 - hydroxy-  
30 pentyl.

The symbol R<sub>4</sub> advantageously represents a hydrogen atom or an alkoxy group

[Price 4s. 6d.]

containing 1 to 4 carbon atoms, such as methoxy, ethoxy, *n* - propoxy- isopropoxy or *n* - butoxy.

In view of the fact that several asymmetrical carbon atoms are involved in the synthesis of the active compounds, the latter may be in the form of racemate mixtures, pure racemates or as optical antipodes. They preferably belong to the laevorotatory series.

As salts of the aforesaid compounds there may be mentioned, for example, basic, neutral, acid or mixed, physiologically tolerable acid addition salts which may also be present as hemi-, mono-, sesqui- or poly - hydrates. Acids suitable for forming these salts are, for example, mineral acids, such as hydrochloric acid, hydrobromic acid, sulphuric or phosphoric acids, nitric acid or perchloric acid, or aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulphonc acids, such as formic, acetic, propionic, oxalic, succinic, glycollic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, dihydroxymaleic or pyruvic acid; phenylacetic, benzoic, *p* - amino-benzoic, anthranilic, *p* - hydroxy - benzoic, salicylic or *p* - aminosalicylic acid, methanesulphonic, ethanesulphonic, hydroxyethane - sulphonic or ethylenesulphonic acid; toluenesulphonic, naphthalenesulphonic acids or sulphanilic acid; or methionine, tryptophane, lysine or arginine.

It is known that domestic animals are exposed to manifold environmental influences which, in certain cases, may produce an undesirable retardation in growth and a considerable increase in feed intake.

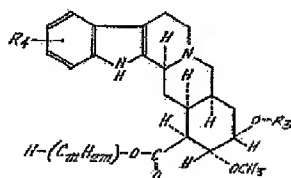
Recently it has been shown that antibiotics, chemotherapeutics, hormone - active agents or *Rauwolfia* diester - alkaloids have a favourable influence on the rearing of domestic animals or increase the degree to which feedstuffs are converted.

It is also known to use *Rauwolfia* diester - alkaloids, such as reserpine, for quieting animals, since the handling of domestic animals, especially poultry, for example for transport, vaccination, debeaking or killing, is still a major problem for the rearer and often involves injuries, that is to say economic losses.

The advantage of the *Rauwolfia* diester - alkaloids over other natural or synthetic, quieting or growth - promoting agents is above all the small dosage, so that especially the meat of the animals so-treated contains practically no trace of the compounds and there is consequently no diminution in quality. These advantages are, however, also offset by certain drawbacks. For example, the onset of the desired quieting effect occurs only after several hours and lasts for a long period, often for days. If, for example, the feedstuffs containing the aforesaid alkaloids are to be administered to facilitate the catching of animals, it is only possible to start catching the animals 4 to 6 hours after feeding them. On the other hand, the long duration of effect can, in some cases, lead to cumulative effects, which has some disadvantages particularly as regards the growth of the animals. A too pronounced tranquillizing of the animals impairs the normal intake of food. In addition, the *Rauwolfia* diester - alkaloids are practically insoluble in water, so that they are not suitable for use in drinking water. This form of administration is desirable, though, on account of a simple method of dosage, uniform distribution among all the animals in a flock or herd and controllability. For example, by withdrawing the drinking water over a certain time and then applying an aqueous solution of the tranquillizing agent, it would be possible to obtain easily a uniform effect over a whole flock or herd.

It has now been found that the aforesaid active compounds used in the preparations of the invention also have the high pharmacological activity of the *Rauwolfia* diester - alkaloids, such as reserpine. In contrast to the latter with their slow onset of effect and often undesirably long duration of pharmacological action, the new compounds show a much more rapid onset and the effect lasts over a well-defined period. Their effect usually does not last longer than 24 hours, that is the effect has completely subsided after this period. In addition, the new compounds, particularly their acid addition salts, are relatively water-soluble and are therefore especially suitable for use in drinking water. They are consequently superior to the known *Rauwolfia* diester-alkaloids.

Especially valuable compounds are those of the formula II

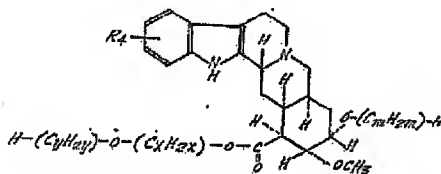


## II

and their acid addition salts, in which formula  $R_5$  stands for  $-(C_nH_{2n})-H$ , each of the symbols  $m$  and  $n$  represents an integer from 1 to 7, preferably from 1 to 3, and  $R_4$  stands for alkoxy containing 1 to 4 carbon atoms, preferably for methoxy,  $R_5$  being especially in one of the positions 10 or 11. Special mention may be made of the highly active methyl 18 - epi - O - R - reserpates in which R stands for methyl, ethyl,  $n$  - propyl or iso - propyl, and their acid addition salts, particularly the hydrochlorides, sulphates or maleates.

Another preferred group of particularly valuable compounds are those of the formula II and their acid addition salts in which  $R_5$  stands for the radical  $-(C_nH_{2n})-OH$ ,  $n$  for an integer from 2 to 7, preferably from 2 to 5, the 18-O-atom being separated from the hydroxyl group by at least 2 carbon atoms, and  $m$  and  $R_4$  having the meanings given above.

Also compounds of the formula III



## III

and their acid addition salts may be especially mentioned, in which formula  $y$  represents an integer from 1 to 4 and  $x$  is 2 or 3, the oxygen atoms adjacent to the group  $-(C_xH_{2x})-$  being separated by at least 2 carbon atoms, and  $m$  and  $R_4$  have the meanings given for formula II.

In domestic animals, such as cattle, horses, sheep, goats or pigs, and particularly in poultry, such as chickens, turkeys, geese or ducks, or in dogs, cats or parrots, the onset of the desired quieting effect occurs shortly after the feedstuffs containing the new compounds have been administered. The animals can then be caught readily and can be treated without undue excitement. Furthermore, the application of feedstuffs or drinking water containing the new compounds to herds or flocks facilitates the handling of the animals, eliminates or minimizes mass hysteria, facilitates the slaughtering process, reduces the work of the personnel and increases their safety, and the injuries caused by excited animals can be avoided.

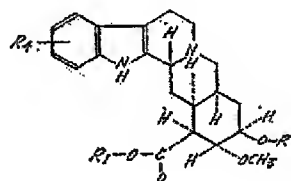
When the feed or drink preparations are administered for the purpose of increasing the food conversion, the aforesaid cumulative effects hardly occur owing to the well-defined duration of effect.

Although it is possible to administer the compounds in single doses to the domestic animals, it is more practical to mix the active ingredient with the feedstuffs or to dissolve them in drinking water. The type of feed components, apart from the active ingredient, depends on the particular animal being fed, the age, the market price of the feedstuffs and other factors. Generally, feedstuffs which contain carbohydrates, proteins, fats, minerals and vitamins are very advantageous. Suitable feed components are, for example, corn, such as rye, wheat, barley, oats, buckwheat, maize, sorghum or millet and their ground products, such as groats, middlings, flakes, shorts or meal, also grass, clover, alfalfa, cabbage or hay, molasses, meat offals, fish-, soyabean-, ground nut- or oil cake-meal, cod liver oil, limestone or bone meal, iodized salt,

dicalcium phosphate or manganese sulphate, vitamins, for example vitamin A, B<sub>12</sub> or D, niacin, thiamine, riboflavin, calcium pantothenate, ascorbic acid or similar feed, mineral and vitamin supplements. In addition, the feedstuffs or drinkable preparations may also contain other valuable ingredients, for example butylated hydroxy-toluene, methionine or antibiotics, for example bacitracin, penicillins, tetracyclines, such as chlortetracycline or oxytetracycline or erythromycin or compounds with a hormone activity, such as diethylstilbestrol or hexestrol.

The feedstuffs usually contain suitable blenders, for example wheat middlings, starches, sugar, such as sucrose or lactose, mannitol, sodium gluconate or soyabean extraction residues. They may also contain buffers, such as citric acid-sodium citrate, sodium acetate, phthalic acid-potassium phthalate, benzoic acid-sodium benzoate, lactic acid-sodium lactate or fumaric acid-sodium fumarate and/or sequestering agents, such as ethylene diamine - tetraacetic acid or the sodium salt thereof, or other useful substances, such as antioxidants or stabilizers. The active compounds may also be used in solution or dispersion in drinking water or skimmed milk, or in any other forms.

The aforesaid compounds used as active ingredients may be obtained by the process described in Applications Nos. 28117/61 (Serial 999,391) and 28119/61 (Serial 999,393) by subjecting a compound of the formula IV



IV

in which R<sub>1</sub> and R<sub>2</sub> have the aforesaid meanings, and R represents the acyl residue of an organic sulphonic acid, or an N-oxide or salt of such a compound, to alcoholysis with an alkanol or a hydroxy-alkanol, and if desired, converting a resulting tertiary amine into an N-oxide, and/or converting a resulting base into a salt or a resulting N-oxide into a tertiary amine, and/or a resulting salt into a free compound.

It has also been found that the feedstuffs preferably contain the active ingredient in an amount between about 0.000005 and 0.1%, advantageously between 0.00001 to 0.025%, for example 0.0005 and 0.01%, by weight. Feedstuffs which are intended to bring about a better food conversion contain, of course, a smaller content of the active ingredient than those intended for tranquillizing. The difference in concentration is approximately two powers of ten. For example, the first mentioned feedstuffs, particularly for poultry, contain from 0.00001 to 0.001% by weight of active ingredient, whereas those intended to bring about a rapid tranquillization contain from 0.001 to 0.1%, preferably from 0.001 to 0.025%, by weight of active ingredient. In addition, the content of active ingredient depends on the body weight of the animals. Poultry, for example chickens, have a proportionally greater food-intake than larger animals, such as cattle or horses. Consequently, the concentration of the active ingredient in feeds for poultry should be less than in that for larger animals.

When the aforesaid compounds are added to drinking water, their concentration therein is advantageously from about 0.00001 to 0.1%, by weight. When the drinking water is given for the purpose of bringing about better food conversion, a content of active ingredient of 0.00001 to 0.001% by weight is sufficient, whereas solutions having a tranquillizing effect advantageously contain 0.001 to 0.1%, preferably 0.001 to 0.025%, for example 0.001 to 0.02%, by weight of active ingredient.

The following Examples illustrate the invention.

## EXAMPLE 1.

Feedstuff for tranquilizing poultry:

*Chief ingredients (premix)*

5	methyl 18 - epi - O - methyl - reserpate hydrochloride	44.000 g	
	Wheat Standard Middlings 30-80 mesh/inch	10,956.000 g	5
	Total Weight	11,000.000 g	

*Feed Formula*

	Corn Meal		
	Fat	1,062.875 g	
10	Fish Meal 60% protein	80.000 g	
	Soyabean Meal 50% protein	100.000 g	10
	Corn Gluten Meal	500.000 g	
	Dehydrated Alfalfa Meal	100.000 g	
	Corn Distiller Solubles	50.000 g	
15	Di-Calcium Phosphate	40.000 g	
	Calcium Carbonate	28.000 g	15
	Iodized Salt	20.000 g	
	Vitamins A & D (1,000,000 International Units of A & 250,000 International Units of D/pound)	10.000 g	
20	Calcium Pantothenate	4.000 g	
	Butylated Hydroxy Toluene	0.250 g	20
	Choline Chloride (crude aqueous preparation containing 25% pure choline chloride)	0.250 g	
	Riboflavin Conc. (24 g per pound)	2.500 g	
25	Vitamin B <sub>12</sub> (0.02 g per pound)	0.125 g	
	Methionine	1.000 g	25
	Manganese Sulphate	0.500 g	
		0.500 g	
	Total Weight	2,000.000 g	

The additives are mixed as follows:

30	About half of the corn meal is introduced into the blending machine, the remainder is added blended with the pre-heated, liquefied fat, and mixing is continued until uniformity is obtained. The manganese sulphate, di-calcium phosphate, calcium carbonate and iodized salt are then added with mixing, followed by the addition of the fish meal, soyabean meal, corn gluten meal, the alfalfa meal and corn distiller solubles. After mixing thoroughly, vitamins A and D, calcium pantothenate, choline chloride, riboflavin, Vitamin B <sub>12</sub> and methionine are added in that order. Mixing is continued after the addition of butylated hydroxy - toluene, and maintained until a uniform product is obtained.	30
35		35

40	The well mixed chief ingredients are then added to the uniform feed formula product in an amount sufficient to provide a concentration of 0.05 grams of methyl 18 - epi - O - methyl - reserpate hydrochloride per 1000 grams of feed in the uniformly blended mix.	40
----	---	----

## EXAMPLE 2.

Drinking water with a tranquilizing effect.

45	0.06 Gram of methyl 18 - epi - O - n - propyl - reserpate hydrochloride is shaken with sufficient water to ensure complete solution. Water is added to bring the volume to a total of 1000 cc.	45
----	--	----

In an analogous manner a solution of 0.015% strength of methyl 18 - epi - O - methyl - reserpate hydrochloride may be prepared.

## EXAMPLE 3.

50	Feedstuff additive.	50
----	---------------------	----

*Ingredients*

	Methyl 18 - epi - O - methyl - reserpate hydrochloride	23.00 g	
	Cane sugar	100.00 g	
55	Soyabean residues (after extraction)	877.00 g	55
	Total	1000.00 g	

The ingredients are thoroughly mixed, and the mixture can then be added in the desired quantity to any feedstuffs. The following feed formula is given as an example:

<i>Ingredients</i>		
5	Alfalfa Meal	50.00 g
	Corn, Yellow	1215.00 g
	Corn Gluten Meal	50.00 g
	Animal Fat	40.00 g
	Dried Distillers Grains	25.00 g
	Fish Meal	100.00 g
10	Oyster Shell	15.00 g
	Poultry By-product Meal (dried and ground poultry trimmings)	100.00 g
	Soyabean Meal	380.00 g
	Sodium Chloride	5.00 g
	Trace Mineral Premix	0.50 g
15	Di-calcium phosphate	15.00 g
	Vitamin Premix	5.00 g
		<hr/> 2000.50 g

The above feedstuff additive is added to the well mixed feed ingredients in a quantity sufficient to obtain a feed containing 0.05% of active ingredient.

20 **EXAMPLE 4.** 20

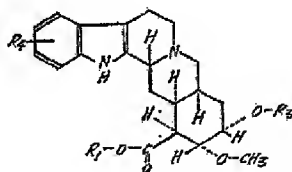
Additive for drinking water.

<i>Ingredients</i>		
25	Methyl 18 - epi - O - methyl - reserpate hydrochloride	30.00 g
	A mixture of 93 per cent of the tetrasodium salt of ethylene-diamine tetra-acetic acid and 7 per cent of the monosodium salt of N:N - di - (2 - hydroxyethyl) - glycine	30.00 g
	Citric acid, anhydrous	70.00 g
	Sodium citrate USP	50.00 g
	Sucrose	120.00 g
30		<hr/> 300.00 g

In order to prepare drinking water with a tranquillizing effect having a content of 0.015% of the active ingredient, 1.5 grams of the above additive are dissolved while stirring well in a little water, and water is then added to bring the volume to a total of 1000 cc.

35 **WHAT WE CLAIM IS:—** 35

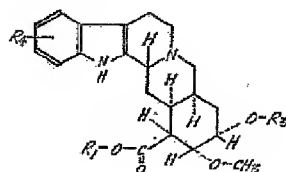
1. An animal feed preparation, which comprises a compound of the general formula V



V

40 in which R<sub>1</sub> represents an alkoxy - alkyl group, as hereinbefore defined, or an alkyl group, R<sub>2</sub> represents a hydroxyalkyl group, as hereinbefore defined, or an alkyl group, and R<sub>3</sub> represents a hydrogen atom or an alkoxy group, or an N-oxide thereof or a physiologically tolerable salt of either compound, in admixture or conjunction with a solid feedstuff. 40

45 2. An animal drink preparation, which comprises a compound of the general formula V 45



in which  $R_1$  represents an alkoxy-alkyl group, as hereinbefore defined, or an alkyl group,  $R_2$  represents a hydroxyalkyl group, as hereinbefore defined, or an alkyl group, and  $R_3$  represents a hydrogen atom or an alkoxy group, or an N-oxide thereof or a physiologically tolerable salt of either compound, in admixture or conjunction with water.

3. An animal feed preparation as claimed in claim 1, comprising 0.000005 to 0.1% by weight of a compound as defined in claim 1 in admixture or conjunction with a solid feedstuff.

4. An animal feed preparation as claimed in claim 3, containing 0.00001 to 0.025% by weight of a compound as defined in claim 1.

5. An animal feed preparation as claimed in claim 4, containing 0.00001 to 0.001% by weight of a compound as defined in claim 1.

6. An animal feed preparation as claimed in claim 3, containing 0.001 to 0.1% by weight of a compound as defined in claim 1.

7. An animal feed preparation as claimed in claim 6 containing 0.001 to 0.025% by weight of a compound as defined in claim 1.

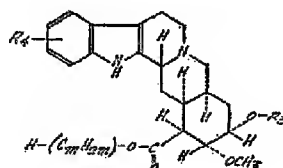
8. An animal drink preparation as claimed in claim 2, comprising 0.00001 to 0.1% by weight of a compound as defined in claim 2 in admixture or conjunction with water.

9. An animal drink preparation as claimed in claim 8, containing 0.00001 to 0.001% by weight of a compound as defined in claim 2.

10. An animal drink preparation as claimed in claim 8, containing 0.001 to 0.1% by weight of a compound as defined in claim 2.

11. An animal drink preparation as claimed in claim 10, containing 0.001 to 0.025% by weight of a compound as defined in claim 2.

12. An animal feed or drink preparation as claimed in any one of claims 1 to 11, wherein the active ingredient is a compound of the general formula II

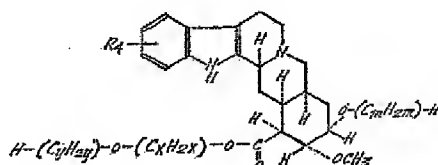


## II

or a physiologically tolerable acid addition salt thereof, in which  $R_3$  represents  $-(C_nH_{2n})-H$ ,  $m$  and  $n$  each represents an integer from 1 to 7 and  $R_4$  represents an alkoxy group containing 1 to 4 carbon atoms.

13. An animal feed or drink preparation as claimed in any one of claims 1 to 11, wherein the active ingredient is a compound of the general formula II shown in claim 12 or a physiologically tolerable acid addition salt thereof, in which formula  $R_3$  represents  $-(C_nH_{2n})-OH$ ,  $n$  represents an integer from 2 to 7, the 18-O atom being separated from the hydroxyl group by at least 2 carbon atoms, and  $m$  and  $R_4$  have the meanings given in claim 12.

14. An animal feed or drink preparation as claimed in any one of claims 1 to 11, wherein the active ingredient is a compound of the general formula III



or a physiologically tolerable acid addition salt thereof, in which  $m$  represents an integer from 1 to 7,  $y$  represents an integer from 1 to 4 and  $x$  represents 2 or 3, the oxygen atoms adjacent to the group  $-(C_3H_2)_x-$  being separated by at least 2 carbon atoms, and  $R_1$  represents an alkoxy group containing 1 to 4 carbon atoms.

15. An animal feed or drink preparation as claimed in any one of claims 1 to 11, wherein the active ingredient is methyl 18 - epi - O - methyl - reserpate or a physiologically tolerable acid addition salt thereof.

16. An animal feed or drink preparation as claimed in any of claims 1 to 11, wherein the active ingredient is methyl 18 - epi - 0 - ethyl - reserpate or a physiologically tolerable acid addition salt thereof.

17. An animal feed or drink preparation as claimed in any one of claims 1 to 11, wherein the active ingredient is methyl 18 - *epi* - O - *n* - propyl - reserpate or a physiologically tolerable acid addition salt thereof.

18. An animal feed or drink preparation as claimed in any one of claims 1 to 11, wherein the active ingredient is methyl 18 - epi - 0 - isopropyl - reserpate or a physiologically tolerable acid addition salt thereof.

19. An animal feed preparation as claimed in claim 1, containing 0.0005 to 0.01% by weight of a compound as defined in any one of claims 12 to 18.

20. An animal drink preparation as claimed in claim 1, containing 0.001 to 0.02% by weight of a compound as defined in any one of claims 12 to 18.

21. An animal feed preparation having a composition substantially as described in Example 1 or 3 herein.

22. An animal drink preparation having a composition substantially as described in Example 2 or 4 herein.

**ABEL & IMRAY,**  
Chartered Patent Agents,  
Quality House, Quality Court, Chancery Lane, London, W.C.2.